Flavonoid Therapy in Diabetic Retinopathy

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• **A new flavonoid, CVP (citrus vitamin P) had no beneficial effect on diabetic retinopathy in 33 patients. Minor improvement in retinal status occurred in 27 per cent of the patients. This rate of improvement is the same as that previously reported after many different therapies, and probably represents spontaneous variation in the course of this disease.**

DIABETIC RETINOPATHY is reversible. Spontaneous involution of microaneurysms, hemorrhages and exudates has been noted by many observers.* Such improvement is usually partial and temporary, occurring only in patients with mild or moderate retinopathy. Complete remission of advanced diabetic retinopathy, the ultimate goal, was first reported by Green[20] in 1950 following adrenalectomy, and later by Poulsen[41] in a case in which postpartum necrosis of the pituitary gland had occurred.

Surgical attempts to induce similar remissions in patients with advanced retinopathy have been the subject of optimistic reports. In describing the results of hypophysectomy in 20 diabetics, Luft and co-workers[34] stated that in the 12 surviving patients, ". . . except for occasional retinal hemorrhages, no symptoms or signs of progression of the diabetic retinopathy were evident. . . . Improvement in visual capacity and/or eyeground changes were noted in most cases." Similar results were described by Kinsell and associates after hypophysectomy in seven diabetic patients. Gordon[17] said that in eight patients surviving hypophysectomy, ". . . striking improvement in the retinopathy has occured uniformly." Schimek[46] reported that five diabetic patients had clearing of hemorrhages after hypophysectomy, but exudates and retinitis proliferans remained unchanged. Headstream and Wortham[22] noted improvement in the retinopathic state in six of seven patients subjected to adrenalectomy. Graef[19] and Malins[35] also reported upon use of adrenalectomy for diabetic vasculopathy.

Follow-up observations have dimmed the hopes of these investigators,[36] except for Gordon, who remains convinced that worthwhile improvement follows hypophysectomy, and Luft, who said that a second series of hypophysectomies is now being done in Sweden, using the antral approach to the hypophysis.[36]

Medical attempts to reverse the ravages of diabetic retinopathy have been unrewarding thus far. In recent years many forms of therapy have been tried, with unimpressive results (Table 1).

In widest use today is a flavonoid, rutin. Interest in flavonoids was first kindled by Szent-Gyorgi's isolation in 1936 of a compound from lemon juice and from Hungarian red pepper (paprika) which he felt was useful in purpura unresponsive to vitamin C. Originally labeled *citrin*, it was later called *hesperidin* or "vitamin P," the "permeabilitats vitamin." Rutin, an analogue of hesperidin, subsequently gained wide usage in an amazing array of unrelated diseases in which capillary fragility supposedly played a role. Johnson[28] in 1946 estimated that 1,300,000 pounds of rutin would be required annually.

The shakily founded early enthusiasm for rutin as a capillary cure-all prompted the American Medical Association Council on Pharmacy and Chemistry (1946)[9] to review the experience with hesperidin. This review reached the conclusion that "Carefully controlled experimental and clinical studies on this substance failed to substantiate the claims ad-

TABLE 1.—*Therapeutic Results Reported From the Literature.*

Treatment	Number of Patients	Percentage of Patients "Improved"
High protein diet[47]	6	67
Carbazochrome[29]	13	0
Lipotropics[15]	50	0
Cysteine[39]	Not stated	0
Cyanocobalamin[3]	Not stated	0
Alpha Tocopherol[10]	12	0
Testosterone[4]	40	0
Testosterone[45]	28	33
Androstenediol[21]	27	0
Estrogen[4]	20	0
X-irradiation of retina[48]	52	33
Trypsin[49]	18	0
Hesperidin[42]	22	23
Rutin[40]	36	22
Rutin[33]	12	42
Rutin[14]	25	0
Rutin[2]	40	25
Rutin[1]	32	0
Rutin[16]	10	0
Rutin[44]	20	0

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*References 4, 11, 33, 37, 42.

vanced," and expressed the hope ". . . that history will not repeat itself with rutin." This proved to be a vain hope indeed.

During the next four years a steady stream of reports† described results of rutin therapy in diabetic retinopathy which were anything but inspiring, and culminated in an exhaustive, independent evaluation of rutin published by the A.M.A. Council on Pharmacy and Chemistry in 1950.[7] The experiments showed it was unlikely that the flavonoids exert any specific chemical or therapeutic effect, or that they are even absorbed from the gastrointestinal tract.

Undaunted by all the weighty evidence of its worthlessness, rutin rolled on, and the present rate of production is a million dollars' worth per year, at the manufacturer's level.[27]

The pertinacity of the flavonoids and the claims made for them, including statements that they are ". . . supplementary therapy of value in virtually all diseased states and specific in action with respect to some"[38] led to a third Council report in 1957.[8] The evidence was again reviewed, with the conclusion that ". . . the flavonoids are of little or no value in the treatment of disease." It was pointed out that ". . . reluctance of individuals to publish negative findings has resulted in a more favorable literature than is deserving."

THE PRESENT STUDY

Prompted by the latter observation, we should like to present the results of our study with the newest of the flavonoids, CVP (citrus-vitamin P), in diabetic retinopathy. CVP* is not a compound of defined chemical structure, but a complex of water-soluble flavonoids which occur naturally in citrus peel and pulp. CVP was administered in a dosage of one capsule three times daily, each capsule containing 100 mg. of water-soluble flavonoid complex and 100 mg. of ascorbic acid. Many patients also received a lipotropic preparation which was considered to play no role in the results, since lipotropic compounds have previously been shown to be without effect in diabetic retinopathy.

Each patient was examined at intervals of three to six months, and the periods of observation ranged from three to thirty-six months. Serial funduscopic sketches were made, as an objective record of the changes which occurred, to avoid basing conclusions on subjective impressions by the examiners. Severity of the retinopathy was graded according to Wagener's classification,[8] and improvement was based on the disappearance of any lesion, either microaneurysm, exudate or hemorrhage, provided new lesions did not appear.

†References 1, 2, 12, 14, 16, 26, 33, 40, 44.

*Manufactured by U. S. Vitamin Corporation.

TABLE 2.—*Results of Citrus Vitamin P (CVP) Therapy in Diabetic Retinopathy.*

Retinopathy Group Grading (Wagener)	Number of Patients	Number Improved
0-I	9	4
II	10	2
III	4	1
IV	2	1
V	8	1
Total	33	9 (27%)

The results are set forth in Table 2. It is of interest that improvement occurred most frequently in the patients in Group O-I, in whom characteristically the early lesions of diabetic retinopathy may come and go in erratic fashion for several years.

In comparing the results with those obtained with other forms of therapy a striking fact emerged: No matter which treatment was used, "improvement," if it occurred at all, is usually reported in one-quarter to one-third of patients (Table 1). In our opinion, this represents the rate of spontaneous temporary remission which will be found in any sizable series of patients with diabetic retinopathy observed for limited periods.

On the basis of the evidence in the literature and our own experience, we believe that the role of flavonoids in the therapy of diabetic retinopathy can be summarized in a single word: None.

DISCUSSION

Late vascular damage has become the most important unsolved clinical problem in diabetes.[13] Therapy with diet and insulin has preserved diabetic persons from early death due to coma, and delivered them to a fate of almost inevitable blindness and death in uremia.

Prevention of diabetic vasculopathy is generally sought by the only means at hand: Meticulous control of the diabetes. There is still doubt in some quarters as to the efficacy of this approach.[49] Therapeutic attack on the problem of diabetic retinopathy is going forward on two main fronts. The first is based on the presumed role of pituitary and adrenal hormones. Circumstantial evidence supplied by the brilliant results sometimes observed after pituitary or adrenal ablation is quite compelling. Further support has come from the experimental production of diabetic retinopathy and glomerulosclerosis in alloxanized animals treated with steroids and pituitary extracts.[39]

Doubts regarding the etiologic role of the pituitary-adrenal axis have been raised by observations that retinopathy is uncommon in the steroid diabetes of Cushing's disease[43] and that it does occur in patients with hemochromatosis,[32] relapsing pancre-

atitis[25] and total pancreatectomy,[6] in whom diabetes is caused by a straight attack on the pancreas without other endocrine involvement.

There has long been a search for a compound capable of producing "medical hypophysectomy." Estrogen, testosterone, B-hydroxyprogesterone[30] and amphenone[24] have all been shown capable of suppressing adrenocortical activity, but not with a clinically acceptable degree of efficiency and safety. Recent experience with 9-a-fluoro-21-desoxy-Medrol,[31] a steroid devoid of antiphlogistic or metabolic activity in man except for suppression of adrenocorticotropin production, offers some hope that an effective pituitary suppressant may be at hand. This steroid is currently under evaluation in our laboratory.

The second therapeutic attack on diabetic vasculopathy is based on the premise that the basic abnormality is a derangement in lipid metabolism. It is common clinical experience that atherosclerosis occurs prematurely and with great severity in diabetic persons. However, cholesterol and phospholipid levels are not significantly different in diabetic persons than in matched controls. Furthermore, the most characteristic and uniquely diabetic lesions, retinal microaneurysms and nodular glomerulosclerosis, are neither common in atherosclerosis nor lipoidal in composition.[50]

Nevertheless, recent studies have disclosed abnormalities of lipid metabolism which may provide a sound basis for therapy. The content of SF 12-20 lipoproteins is elevated in persons with poorly controlled diabetes, and is even more distinctly increased in those with retinopathy.[43] Levels of esterified fatty acids rise and fall in parallel with the blood sugar in unstable diabetes,[23] and the metabolism of non-esterified fatty acids is abnormal even in cases of controlled diabetes.[5]

Studies are currently under way to evaluate the therapeutic effect of polyunsaturated "essential" fatty acids,[18] and preliminary results are said to be encouraging.

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